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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~_____ days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 17-19 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 17-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 08/433,423 filed on 07/13/95.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Claims 1-16 have been canceled.

Claims 17-19 have been added.

Claims 17-19 are examined on the merits.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should reflect that the claimed invention is drawn to treatment methods and antibody compositions for said therapies.

3. Claims 17-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

Claims 17-19 are vague and indefinite in the recitation "label." The metes and bounds "label" is unknown. The applicant is advised to amend the claim to recite detectable label.

4. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods for the inhibition of the proliferation of human endothelial cell comprising the administration of one of three different three monoclonal antibodies that bind proliferating human endothelial cells, but do not bind to non-proliferating human endothelial cells (1D5, 8G4 and 18C6) (see p. 10 and Table 3), does not reasonably provide enablement for *in vivo* methods of inhibiting angiogenesis and treating tumor associated angiogenesis in human patients comprising the administration of antibodies that bind to proliferating human endothelial cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A. Claim 17 is drawn to "therapeutic composition for inhibition of tumor associated angiogenesis or the treatment of tumor associated angiogenesis," which is broadly interpreted to read on *in vivo* methods for treating human patients. The methods of claim 18, drawn to a "method for inhibition of angiogenesis in a patient, said angiogenesis being associated with the growth of solid tumors," and claim 19, drawn to a "method for treatment of tumor associated

predictability. *In vitro* assays depend on cell culture and therefore do not entirely simulate *in vivo* conditions. *In vitro* assays cannot easily assess additional factors that may be important in a particular disease state. Further, in order to be effective, a therapeutic agent must reach and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the therapeutic agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. The observations of Matsuzaki (PNAS 86:9911, 1989), that two different monoclonal antibodies that inhibit the growth *in vitro* of cultured endothelial cells do not inhibit the *in vivo* growth of tumors, but rather induce the growth of highly vascularized tumors (see abstract), are cited to support the lack of generalizability from successful *in vitro* results to successful *in vivo* results.

C. Claims 17-19 are broadly drawn to antibodies "which specifically bind proliferating human endothelial cells." Other than binding to proliferating endothelial cells, the specification provides no guidance for selecting antibodies that can effectively be used in methods of treating tumor associated angiogenesis and inhibiting angiogenesis. Of the 1087 such monoclonal antibodies that bind to proliferating endothelial cells presented in the specification, only three demonstrate the *in vitro* ability to inhibit endothelial cell proliferation. Claims 17-19 also include antibodies "which specifically bind proliferating human endothelial cells" that have been conjugated to one of many toxins. Press et al (J. Immunol. 141:4410, 1988) notes that three antibodies that bind to different epitopes of the same cell surface molecule (CD2), when conjugated to toxins demonstrate markedly different efficacies in anti-tumor effect. Press concludes that different antibody-immunotoxin conjugates (an IT-A) "targeting the same surface molecule can differ markedly in potency, and that the epitope recognized by an IT-A may have a significant impact on the ability of the IT-A to insert into cell membranes, translocate to the cytosol, and kill cells." The specification provides no instruction as to the epitope, or even the cell surface molecule recognized by the antibodies used in the claimed treatment methods. Thus, one of skill in the art could not make and use the claimed invention without undue

angiogenesis in patient" are also broadly interpreted to read on *in vivo* therapeutic treatments of humans. Thus, the claimed invention pertains to the highly experimental and unpredictable field of *in vivo* human therapy using monoclonal antibodies. Harris, Hird and Dillman are cited in order to establish the general state of the art and level of predictability of treating human cancers *in vivo* using monoclonal antibodies. The general lack of established clinical protocols for effective monoclonal antibody-based therapy of human diseases and the high degree of unpredictability of the art to which the invention pertains, provide reasonable doubt as to the accuracy of applicant's assertion that the claimed methods can be used to effectively treat angiogenesis-dependent diseases in humans in the absence of convincing experimental evidence which establishes the efficacy of the claimed methods. Harris teaches that there is widespread acceptance in the art that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy. Harris cites several problems limiting the effective use of rodent monoclonal antibodies including (1) short in vivo half-life; (2) poor recognition of rodent immunoglobulin constant regions with human effector cells and (3) the human immune response (HAMA) against murine proteins. Anti-murine antibodies elicited in the HAMA response complex with administered antibodies and have the effect of rendering repeated antibody dosing ineffective.

B. In support of the broadly drawn treatment methods, the specification teaches that three antibodies with specificity for proliferating human endothelial cells inhibit the proliferation of HUVEC cells cultured *in vitro* (see pages 9-10). On the basis of this observation alone, the applicant concludes that antibodies with a general specificity for proliferating human endothelial cells can be administered to humans to effectively treat tumor associated angiogenesis and inhibit angiogenesis *in vivo*. The applicant has not presented sufficient evidence to give one skilled in the art a reasonable expectation of using the claimed antibody compositions and methods to effectively inhibit angiogenesis-dependent tumor growth. Those of skill in the art recognize that clinical correlations are usually lacking with *in vitro* assays such as those exemplified in the specification. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay, does not permit a simple extrapolation of *in vitro* assays to human therapeutic efficacy with any reasonable degree of

experimentation and one of skill in the art would not have a reasonable expectation of success when practicing the invention commensurate with the scope of the claims.

D. Applicant's specification does not set forth sufficient direction or guidance to enable one skilled in the art to effectively practice the claimed methods. The specification provides no detailed description of how to effectively administer monoclonal antibodies i.e. effective dosages which are critical to achieving an effective therapeutic result. No working examples are provided which would provide sufficient guidance to allow one skilled in the art to use of antibodies with the claimed specificity for the effective treatment of angiogenesis-dependent diseases with a reasonable expectation of success.

The specification does not adequately teach how to effectively use the claimed methods for the use of antibodies specific for proliferating/angiogenic human endothelial cells as agents for the treatment of angiogenesis-dependent diseases in patients. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting angiogenesis associated with tumor growth in a patient and for treating tumor associated angiogenesis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claim 17 is rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,512,660 (04/30/96, effective filing date of at least 12/22/89) as evidenced by "Hemostasis and Thrombosis." The '660 patent discloses therapeutic compositions of antibodies (both polyclonal and monoclonal) that specifically bind to human ICAM-2 (see col. 4, lines 29-24), including conjugates of said antibodies to toxins such as ricin and radioisotopes (see col. 8, lines 46-56) together with a pharmaceutically acceptable carrier (see col. 22, line 20) that are the same as that claimed. Patent '660 does not disclose that antibodies to human ICAM-2 specifically bind to proliferating human endothelial cells. However, this is an inherent property of the disclosed antibodies, as evidenced by Hawiger. Hawiger notes that ICAM-2 is constituently expressed on endothelial cells (see p. 766, col.2). Thus, the antibodies disclosed in patent '660, binding to a molecule constituently expressed by endothelial, bind to proliferating human endothelial cells. The intended use of the claimed composition, "for inhibition of tumor associated angiogenesis or for treatment of tumor associated angiogenesis" is given no patentable weight for the application of art. As a composition is a composition irrespective of what its intended use is (see In re Tuominen, 213 USPQ 89 (CCPA 1982)), for examination purposes, the claim reads on the ingredients of the claimed composition.

7. Claim 17 is rejected under 35 U.S.C. § 102(b) as being anticipated by Brodsky et al (Eur. J. Immunol 9:536, 1979) as evidenced by "Major Histocompatibility Complex" (Ch. 4 of "Immunology," 1989). Brodsky discloses compositions of the monoclonal antibodies BBM.1 (which specifically binds to human β_2-microglobulin) or W6/32 (which specifically binds to an

antigenic determinant shared by human HLA-A, B and C) (see abstract) with PBS, an art known pharmaceutical carrier (see assays, 2.4), that are the same as that claimed. Brodsky does not disclose that BBM.1 and W6/32 specifically bind to proliferating human endothelial cells. However, this is an inherent property of the disclosed antibodies, as evidenced by "Major Histocompatibility Complex." "Major Histocompatibility Complex" notes that human HLA-A, B and C are antigens expressed on all nucleated cells (see Fig. 4.6) and that β_2-microglobulin is an integral component of intact human HLA-A, B and C in the plasma membrane (see Fig. 4.16). Thus, the antibodies disclosed in patent Brodsky, binding to all nucleated human cells, bind to proliferating human endothelial cells. Again, the intended use of the claimed composition, "for inhibition of tumor associated angiogenesis or for treatment of tumor associated angiogenesis" is given no patentable weight in the application of the art.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gougos (J. Immunol. 141:1925, 1988). Gougos teaches the monoclonal antibody 44G4, which binds to human endothelial cells, including endothelial cells from human umbilical cord (see abstract and Table I). Gougos does not teach the 44G4 antibody binding to proliferating endothelial cells or a composition of the antibody with a pharmaceutically acceptable carrier. However, given the teachings in Gougos, that the 44G4 antibody binds to endothelial cells in general, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made, that the antibody would also bind to proliferating endothelial cells. Further, given the teachings in Gougos of the use of the diluted antibody in FACS analyses on intact cells, it would

have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition of the antibody with a pharmaceutically acceptable carrier.

10. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Angiogenesis EXS 61:266-271, April 2, 1992) in view of Harlow and Lane. Wang teaches the monoclonal antibodies E-9, which binds to proliferating human endothelial cells and human umbilical vein endothelial cells (see abstract), and 5.6E, a pan-endothelial anti-CD31 monoclonal antibody (see p. 267). Wang does not teach a composition comprising these antibodies and a pharmaceutically acceptable carrier. However, Harlow and Lane teach the addition of phosphate-buffered saline (PBS) or similar isotonic solutions to antibodies for long term storage (p. 287). Both PBS and similar isotonic saline solutions are art known pharmaceutically acceptable carriers. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to add PBS or another isotonic saline solution to the antibodies taught in Wang. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Harlow and Lane, that such addition facilitates long term storage of antibodies.

11. Claims 17-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hagemeier et al. (Int. J. Cancer Res. 38:481-488, 1986). Hagemeier et al. discloses a composition comprising a monoclonal antibody specific for proliferating human umbilical vein endothelial cells (see abstract) and the pharmaceutical composition, phosphate buffered saline (PBS) (see Immunohistology, p. 481) and therapeutic methods for the treatment of angiogenic-dependent disorders and tumors (see last paragraph, p. 487) comprising the administration of said antibody that are the same as those claimed.

12. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the

"right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

13. A timely filed terminal disclaimer in compliance with 37 CAR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CAR 3.73(b).

14. Claims 17-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,677,181. Claims 1-9 of U.S. Patent 5,677,181 are drawn to antibodies that bind to endothelial cells. Hagemeier teaches the usefulness of antibodies specific for endothelial cells in methods of treatment of tumor-associated angiogenesis (see p. 487). Thus, it would have been *prima facia* obvious to one of ordinary skill in the art to use the patented antibodies of claims 1-9 of U.S. Patent 5,677,181 in the treatment methods taught in Hagemeier. The claimed therapeutic composition of the antibodies (claim 17) is also *prima facia* obvious to one of ordinary skill in the art in view of the teachings of Hagemeier, on the therapeutic usefulness of such antibodies.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Johnson whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. Johnson

Nancy A. Johnson, Ph.D.
Patent Examiner, Group 1806
January 22, 1998